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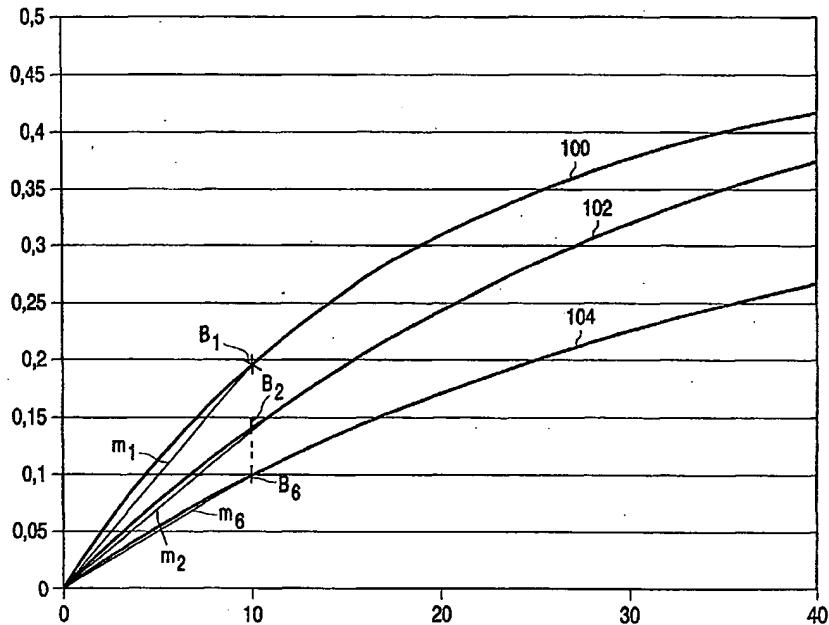
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Declaration under Rule 4.17:

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- (54) Title: A METHOD OF MAGNETIC RESONANCE PERFUSION IMAGING



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- (57) Abstract: The present invention relates to a method of perfusion imaging comprising: performing a first magnetic resonance data acquisition (A) at a first sensitivity (b) value, performing a set of at least six second magnetic resonance data acquisitions (B₁, B₂, ..., B₆) with gradient encodings in different directions at second sensitivity (b) values, determining a perfusion tensor based on the magnetic resonance data acquisitions, performing a perfusion tensor visualization step.



CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
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KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT,
LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF,
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A method of magnetic resonance perfusion imaging

FIELD OF THE INVENTION

The present invention relates to the field of magnetic resonance imaging, and more particularly to perfusion tensor imaging.

5 BACKGROUND AND PRIOR ART

Diffusion weighted magnetic resonance imaging is a known prior art technique. In diffusion weighted magnetic resonance imaging the diffusion tensor is obtained from the magnetic resonance measurement signal for a defined body region of interest. The diffusion tensor is then visualised by known imaging methods (US Patent No. 5,539,310; La Bilhan et al, Diffusion Tensor Imaging: Concepts and Applications, Journal of Medical Resonance Imaging 13:534-46 (2001); Lawrence R. Frank, Anisotropy in High Angular Resolution Diffusion-Weighted MRI, Magnetic Resonance in Medicine 45:935-939 (2001),). An overview of known diffusion-weighted magnetic resonance techniques is provided by Gray L. MacFall J. Overview of diffusion Imaging. Magnetic Resonance Imaging Clin N Am 1998; 6:125-138.

In addition in vivo intravoxel incoherent motion (IVIM) magnetic resonance imaging is a known technique (La Bilhan D et al, MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurological disorders. Radiology 1986;161:401-407.) In particular, the interpretation of IVIM measurements with respect to classical perfusion has been discussed in the prior art (La Bilhan D et al., Separation of diffusion and perfusion in intravoxel incoherent motion MR Imaging. Radiology 1998;168:497-505; Henkelman RM. Does IVIM measure classical perfusion? Magn Reson Med 1990;16:470-475; Le Bilhan D, Turner R. The capillary network: a link between IVIM and classical perfusion. Magn Reson Med 1992;27:171-178). This imaging technique uses gradient encodings for random motion.

Classical perfusion is a measure of the blood delivered to and used by a specified mass of tissue. It is often measured using spin labelling techniques in MRI. In contrast, IVIM measures quasi-random blood movement within a single imaging voxel and results in a bi-exponential signal attenuation in a standard pulsed gradient spin echo (PGSE)

experiment (cf. R.J. Moore et al, *in vivo* intravoxel incoherent motion measurements in the human placenta using echo-planar imaging at 0.5 T, *Magnetic Resonance in Medicine*, 43;295-302 (2000)).

It is a common disadvantage of prior measurement techniques that only a scalar value for the perfusion is obtained even though perfusion usually is anisotropic. A scalar perfusion value therefore only gives a limited amount of information on the actual nature of the perfusion.

Therefore the present invention aims to provide an improved imaging method which enables imaging and visualisation of the perfusion anisotropy as well as a corresponding computer program product and perfusion imaging apparatus.

SUMMARY OF THE INVENTION

The present invention provides for a method of perfusion imaging which can be used for medical purposes such as abdominal imaging.

The present invention is based on the discovery that an isotropic perfusion can be described by a tensor which is structurally equivalent to a diffusion tensor used for diffusion tensor imaging (DTI). In order to provide the data for determination of a perfusion tensor a magnetic resonance data acquisition is performed at a low b sensitivity value, preferably $b=0$, as well as at least six magnetic resonance data acquisitions with gradient encodings in different directions at b sensitivity values of for example below 50 [s/mm²], preferably between 5 and 15.

In accordance with a preferred embodiment of the invention six slopes are determined from the 7 measurement points. The slope values form the basis for calculating the perfusion tensor, especially its eigenvectors. This is based on the discovery, that for lower b sensitivity values the signal decay is mostly due to perfusion and not diffusion effects. This is why diffusion can be neglected at low b sensitivity values in order to extract the information out of the decay signal which forms the basis for determining the shape of the perfusion tensor. At least, the sorting of the eigenvalues and the direction of the eigenvectors of the perfusion tensor does not depend much on the diffusion-related signal decay. This directional information derived from the perfusion tensor can be visualized. For this purpose software algorithms which are used in the prior art for diffusion visualization can be reused due to the same mathematics governing the visualization of diffusion and perfusion tensors.

In accordance with a further preferred embodiment of the invention, two additional magnetic resonance data acquisitions are performed for higher b sensitivity values.

For example one additional magnetic resonance data acquisition is performed for an intermediate b sensitivity value of around 200 and a further magnetic resonance data acquisition is performed at a high b sensitivity value of around 800.

- For such high b sensitivity values the decay signal is mostly governed by its diffusion signal component, see e.g. [Petra Mürtz, et al. Abdomen: Diffusion-weighted MR Imaging with Pulse-triggered Single-Shot Sequences, 258-264, Radiology July 2002]. Especially in the abdomen, the diffusion is isotropic, as demonstrated in the cited reference. Thus, the diffusion coefficient can be obtained from just two higher b-values measurements. For brain imaging it is preferred to perform at least six data acquisitions with gradient encodings for random motion in different directions as diffusion is anisotropic in this case.

- Mathematical analysis also provides the blood fraction value. This fraction is known to be isotropic for each measured signal, thus constraining the analysis. Based on the diffusion coefficient and the blood fraction value the diffusion component of the decay signal can be estimated. By subtracting the diffusion signal component from the measurement signal the perfusion signal component is obtained. The perfusion coefficient is obtained from the perfusion signal component by determining the signal slope of the perfusion signal component, thereto the b=0 and low b-value measurements are analyzed.

- In accordance with a further preferred embodiment of the invention only one additional magnetic resonance data acquisition is performed for a high b sensitivity value, leaving out the intermediary measurement. In this case one of the magnetic resonance data acquisitions which have been performed for the low b sensitivity values having the highest signal value is selected as a replacement for the intermediate measurement.

- It is to be noted that for the intermediate and high b data acquisitions no gradient encodings in different directions are necessary as diffusion is isotropic for such high b values.

- It is a particular advantage of the present invention that due to the limited number of data acquisitions, all of the required data acquisitions can be performed for a couple of slices through the body (typically 5-10) within a single breath hold, for example in less than 16 seconds.

30

BRIEF DESCRIPTION OF THE DRAWINGS

In the following preferred embodiments of the invention will be described in greater detail by making reference to the drawings in which:

Figure 1 is illustrative of a logarithmic diagram showing magnetic resonance imaging signals which form the basis for perfusion tensor determination and imaging,

Figure 2 is illustrative of a flow chart for determining the perfusion tensor based on the signals shown in figure 1,

5 Figure 3 is an enlarged view of the decay curves of figure 1 and is illustrative of a further preferred embodiment of the invention.

Figure 4 is a block diagram of an imaging system.

DETAILED DESCRIPTION

10 The general idea of intra-voxel incoherent motion imaging (IVIM) is that the observed MR signal decay has a bi-exponential behaviour as function of the diffusion weighting factor b, i.e.

$$S/S_0 = A1 * \exp(-b*P) + A2 * \exp(-b*D), \quad (1)$$

where P is the perfusion constant (in mm²/sec, typically 0.05-0.08), and D the diffusion 15 constant (in mm²/sec, typically 0.002).

It can readily be appreciated that (for b=0) A1+A2=1. Thus, recognizing that the signal related to perfusion can be attributed to (randomly) flowing material in the voxel, A1 has been designated to represent f, the fraction of flowing material (i.e. blood) in the voxel. Hence f denotes the blood fraction and A2=1-f, which in other words means that the 20 non-flowing part of the signal contributes to the diffusion signal. The fraction f, being representative of the blood content, is an isotropic quantity for each voxel. This knowledge is used to constrain the data analysis in the rest of this section.

This leads to

$$S/S_0 = f * \exp(-bP) + (1-f) * \exp(-bD). \quad (2)$$

25 The first term of equation 2 will be referred to as the perfusion signal component and the second term in equation 2 will be referred to as the diffusion signal component. The perfusion signal component is decaying much more rapidly than the diffusion signal component and thus primarily determines the slope of the signal for low b values.

The perfusion is described by a perfusion tensor, which has the same structure 30 as the diffusion tensor, i.e. the perfusion tensor is of second rank and symmetric.

The perfusion tensor can be determined on the basis of the bi-exponential signal of equation 2, using the signal decays for low b values whereby the diffusion signal component is neglected. This is illustrated by means of figure 1.

Figure 1 shows signal decay curves 100, 102 and 104 as a function of b. Magnetic resonance image acquisition is performed for $b = 0$ (point A) as well as for lower b-values (points B_1, B_2, \dots, B_6). A good choice for the low b-value is around 10.

As it can be seen from the signal decay curves of figure 1 the curves are
5 approximately linear for low b values.

For the purpose of determining the perfusion tensor the magnetic resonance data acquisition for point A is performed without gradient encoding and for the points B_1, B_2, \dots, B_6 at six different gradient directions, respectively. The slopes m_1, m_2, \dots, m_6 of the signal decay curves for low b-values are determined as illustrated in figure 1 by linear
10 approximation.

By means of the six slope values the perfusion tensor can be calculated by means of the same mathematics as used for diffusion tensor calculation (c.f. for example M.T. Vlaadringenbroek and J.A. den Boer. Magnetic Resonance Imaging. Springer-Verlag Berlin Heidelberg New York, 1999, in particular section 7.7).

15 Figure 2 is illustrative of the corresponding flow chart. In step 200 a magnetic resonance data acquisition is performed for point A (c.f. figure 1) with $b = 0$ without gradient encoding. In step 202 magnetic resonance data acquisition is performed for B_i for a low b value with gradient encoding into a first direction. In step 204 the i is incremented and step 202 is performed again for the next gradient encoding direction. Step 202 is repeated at least
20 6 times for magnetic resonance data acquisitions into at least six different gradient encoding directions.

In step 206 the slope values m_i are obtained from the measurements points A and B_1, B_2, \dots, B_6 by linear approximation, i.e. from the slopes of the straight lines connecting A to B_1, A to B_2, \dots, A to B_6 . These slope values provide full mapping of the perfusion tensor
25 and are input into the perfusion tensor calculation routine of step 208.

For increased precision the diffusion signal component of equation (2) is also taken into consideration for the perfusion tensor determination. One way of accomplishing this is illustrated by making reference to figure 3.

Figure 3 shows the signal decay curves 100 and 102 of figure 1 for higher b-values. As apparent from figure 3 the signal decay curves become approximately a straight line for higher b values.
30

For determination of the diffusion coefficient D two magnetic resonance data acquisitions are performed for b values within the linear portion of the signal decay curves. For example this can be done for $b=200$ (point X) and for $b=800$ (point Y).

The slope of the straight line between points X and Y is the diffusion coefficient D. The extrapolation of the straight line between X and Y to b=0 provides 1-f as illustrated in figure 3. This way the diffusion signal component of equation (2) is obtained. It is to be noted that the extrapolation by means of the straight line is performed for

- 5 convenience of explanation; in a practical application it is preferred to perform the analysis of the bi-exponential decay using well known mathematical routines such as available from the LAPACK mathematical library.

The perfusion signal component is analysed by subtracting the estimated diffusion signal component, i.e. $S_{est} = (1-f) * \exp(-bD)$, from the measured value S. For the b=0
10 value of the curve this provides a value $S_0 * f$, denoted as S_0' . For any signal related to non-zero b-values, a value S' is derived. A new curve can now be drawn to show $\ln(S_0'/S')$. The slope of this curve provides P.

In other words, by subtracting the estimated diffusion signal component, the perfusion signal component is isolated from the measured data values; as f is also known the
15 perfusion coefficient P can be obtained this way.

For example, this enables a pre-processing of the signal decay curves 100, 102, 104, ... of figure 1 by subtracting the diffusion signal component before the determination of the slopes m_i .

Alternatively the perfusion coefficient P is calculated as explained above for
20 every diffusion-sensitisation gradient direction. The resulting set of at least six perfusion coefficients is used to calculate the perfusion tensor map. Specifically, the perfusion tensor's eigenvalues, eigenvectors, and rotationally invariant quantities like the trace or the fractional anisotropy are derived and visualized. Also, voxels with substantially co-linear main eigenvectors can be connected (starting from a user defined seed position), and the
25 connecting line can be displayed (tractography).

In order to avoid the measurement for point X at the intermediate b value it is also possible to use the highest value of the B_1, B_2, \dots, B_6 measurements for low b values as an approximation. In the example considered here the highest value is B_1 (cf. figure 1). In order to obtain an approximation for D and 1-f, a straight line between Y and B_1 can be used
30 instead of a straight line between X and Y.

One of the advantages of keeping the number of high b-value acquisitions at a minimum is that each acquisition prolongs the breath hold duration by typically 1 to 3 seconds. Completely avoiding higher b-value acquisitions enables the use of short echo times, because such high b-value acquisitions require much gradient area, thus having a relatively

long echo time (typically 60-90 ms, whereas T2 relaxation in the abdomen is only 100 ms). The long echo time relative to T2 relaxation significantly lowers the SNR of the measurements. Using only small b values (<50) significantly reduces the required gradient area, and thus enables lower echo times (typically 20-30 ms). This significantly improves the
5 SNR.

Figure 4 shows a block diagram of perfusion imaging system 400. Perfusion imaging system 400 has magnetic resonance data acquisition device 402 which provides magnetic resonance data to computer system 404. For example, the magnetic resonance data acquisition is performed by means of a sequence of single-shot echo-planner MR imaging
10 sequences.

These sequences are determined by control program 406 which controls MR data acquisition device 402 accordingly. The acquired MR data is stored in storage 408. Program 410 analyses the acquired MR data which are stored in storage 408 in accordance with the principles as explained above with reference to figures 1 to 3. This way a perfusion
15 tensor is obtained which is stored in storage 412. The perfusion tensors stored in storage 412 are processed by imaging program 414 which generates a perfusion tensor image which is stored in frame buffer 416 for display on display unit 418 connected to computer system 404.

REFERENCE NUMERALS

20	100	signal decay curve
	102	signal decay curve
	104	signal decay curve
	400	performance imaging system
	402	MR data acquisition device
25	404	computer system
	406	control program
	408	storage
	410	program
	412	storage
30	414	imaging program
	416	frame buffer
	418	display unit

CLAIMS:

1. A method of perfusion imaging comprising:
 - performing a first magnetic resonance data acquisition (A) with gradient encodings for random motion at a first sensitivity (b) value,
 - performing a set of at least six second magnetic resonance data acquisitions (B₁, B₂, ... B₆) with gradient encodings for random motion in different directions at second sensitivity (b) values,
 - determining a perfusion tensor based on the magnetic resonance data acquisitions.
2. The method of perfusion imaging of claim 1, the second sensitivity values being below 50 s/mm² and the first sensitivity value being substantially smaller than the second sensitivity values.
3. The method of perfusion imaging of claim 1 or 2, whereby the first sensitivity value is substantially zero and the second sensitivity values being between five and thirty, preferably ten.
4. The method of perfusion imaging of claims 1, 2 or 3, the magnetic resonance data acquisitions being performed by means of a series of single-shot echo-planar magnetic resonance data acquisitions.
- 20 5. The method of perfusion imaging of any one of the preceding claims 1 to 4, further comprising performing a perfusion tensor visualisation step.
- 25 6. The method of perfusion imaging of claim 5, whereby directional information derived from the perfusion tensor is visualized.
7. The method of perfusion imaging of any one of the preceding claims 1 to 6, further comprising determining of first slope values (m₁, m₂...m₆) between each one of the

set of magnetic resonance data acquisitions ($B_1, B_2, \dots B_6$) and the first magnetic resonance data acquisition (A), and determining the perfusion tensor based on the first slope values.

8. The method of perfusion imaging of any one of the preceding claims 1 to 7,
5 further comprising:
- performing of a third magnetic resonance data acquisition (X) at a third sensitivity (b) value,
 - performing of a fourth magnetic resonance data acquisition (Y) at a fourth sensitivity (b) value, the third sensitivity value being substantially higher than the second sensitivity
10 values, and the fourth sensitivity value being substantially higher than the third sensitivity value,
 - determining of a diffusion coefficient (D) and a fraction value (f) based on the third and the fourth magnetic resonance data acquisitions to provide a diffusion signal component,
 - eliminating of the diffusion signal component from the magnetic resonance data
15 acquisitions to provide a perfusion signal component,
 - determining of a perfusion tensor from the perfusion signal components.

9. The method of perfusion imaging of claim 8, whereby a set of at least six third magnetic resonance data acquisitions with gradient encodings for random motion in different
20 directions at third sensitivity (b) values is performed, and a set of at least six fourth magnetic resonance data acquisitions with gradient encodings for random motion in different directions at fourth sensitivity (b) values is performed, and the diffusion tensor tensor is determined based on the third and the fourth magnetic resonance data acquisitions to provide a diffusion signal component.
25

10. The method of perfusion imaging of claim 8 or 9, the third sensitivity value being between 100 and 400, and the second sensitivity value being between 600 and 1200.

11. The method of perfusion imaging of any one of the preceding claims 1 to 7,
30 further comprising:
- selecting one of the second magnetic resonance data acquisitions ($B_1, B_2, \dots B_6$) having the strongest measured signal decay,
 - performing a third magnetic resonance data acquisition (Y) at a third sensitivity (b) value, the third sensitivity value being substantially higher than the second sensitivity values,

- determining of a diffusion coefficient (D) and a fraction value (f) based on the selected second and third magnetic resonance data acquisitions to provide a diffusion signal component,
 - eliminating the diffusion signal component from the magnetic resonance data acquisitions 5 to provide a perfusion signal component,
 - determining of a perfusion tensor from the perfusion signal components.
12. A computer program product, in particular digital storage medium, for perfusion imaging comprising program means for determining a perfusion tensor based on a 10 first magnetic resonance data acquisition (A) and a set of at least six second magnetic resonance data acquisitions (B_1, B_2, \dots, B_6), the first magnetic resonance data acquisition being performed at a first sensitivity value and the second magnetic data resonance data acquisitions being performed at a second sensitivity value with gradient encodings in different directions, whereby the first sensitivity value is substantially below the second 15 sensitivity values, and for performing a perfusion tensor imaging step.
13. The computer program product of claim 12, the program means being adapted to determine of first slope values (m_1, m_2, \dots, m_6) for each one of the second magnetic resonance data acquisitions (B_1, B_2, \dots, B_6) based on the first magnetic resonance data 20 acquisition (A) and to determine the perfusion tensor based on the first slope values.
14. The computer program product of claims 12 or 13, the program means being adapted to determine a diffusion coefficient (D) and a fraction value (f) based on third (X) and fourth (Y) magnetic resonance data acquisitions to provide a diffusion signal component, 25 to eliminate the diffusion signal component from the magnetic resonance data acquisitions to provide a perfusion signal component, and to determine a perfusion tensor from the perfusion signal component.
15. The computer program product of claim of claim 14, the program means being 30 adapted to process a set of at least six third magnetic resonance data acquisitions with gradient encodings for random motion in different directions at third sensitivity (b) values, a set of at least six fourth magnetic resonance data acquisitions with gradient encodings for random motion in different directions at fourth sensitivity (b) values, and to determine the

diffusion tensor based on the third and the fourth magnetic resonance data acquisitions to provide a diffusion signal component.

16. The computer program product of claims 12 or 13, the program means being
5 adapted to select one of the second magnetic resonance data acquisitions ($B_1, B_2, \dots B_6$) having the highest data value, determining of a diffusion coefficient (D) and a fraction value (f) based on the selected second magnetic resonance data acquisition and a third magnetic resonance data acquisition (Y) being performed at a third sensitivity value, the third sensitivity value being substantially above the second sensitivity values, providing a diffusion
10 signal component based on the diffusion coefficient and the blood fraction value, eliminating of the diffusion signal component from the magnetic resonance data acquisitions to provide a perfusion signal component, and to determine of a perfusion tensor from the perfusion signal components..
- 15 17. A perfusion imaging apparatus comprising:
- means (402, 404, 406, 408) for performing a first magnetic resonance data acquisition (A) at a first sensitivity (b) value and for performing a set of at least six second magnetic resonance data acquisitions ($B_1, B_2, \dots B_6$) with gradient encodings in different directions at second sensitivity (b) values,
20 - means (410, 412) for determining a perfusion tensor based on the magnetic resonance data acquisitions,
- means (414, 416, 418) for performing perfusion tensor imaging.

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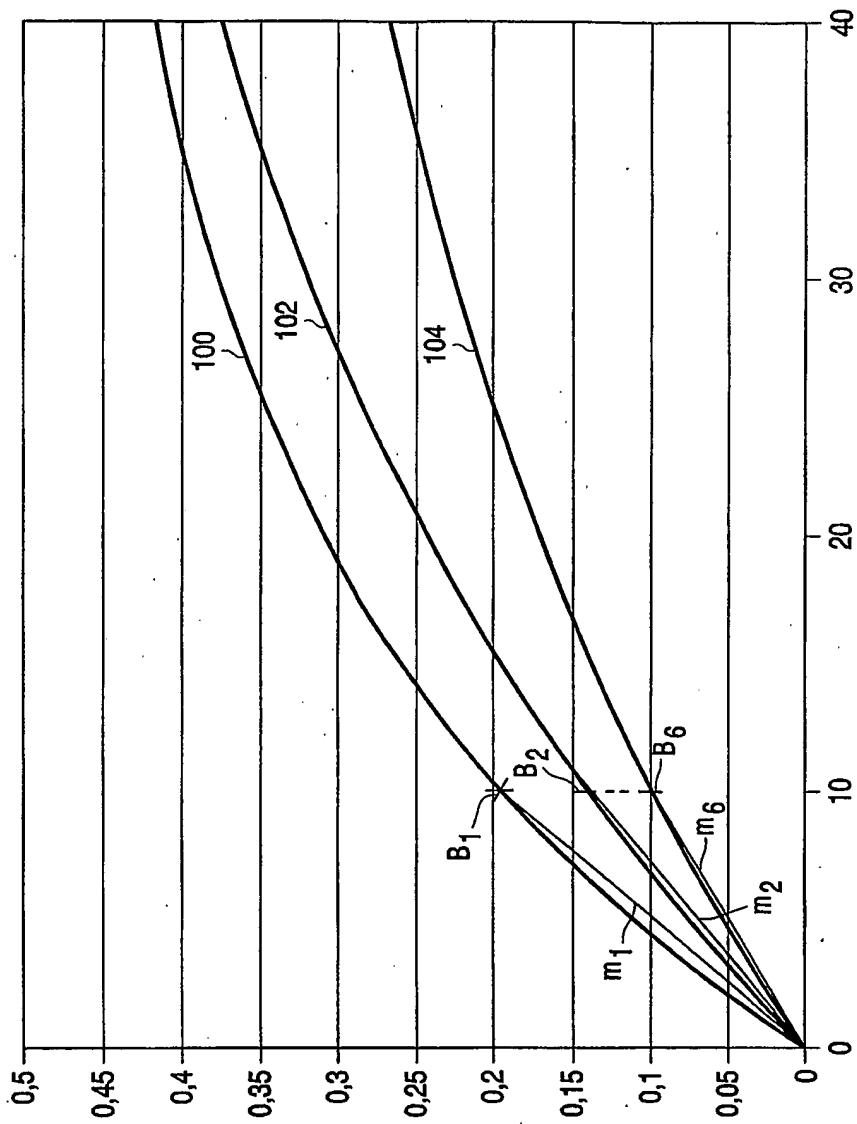


FIG. 1

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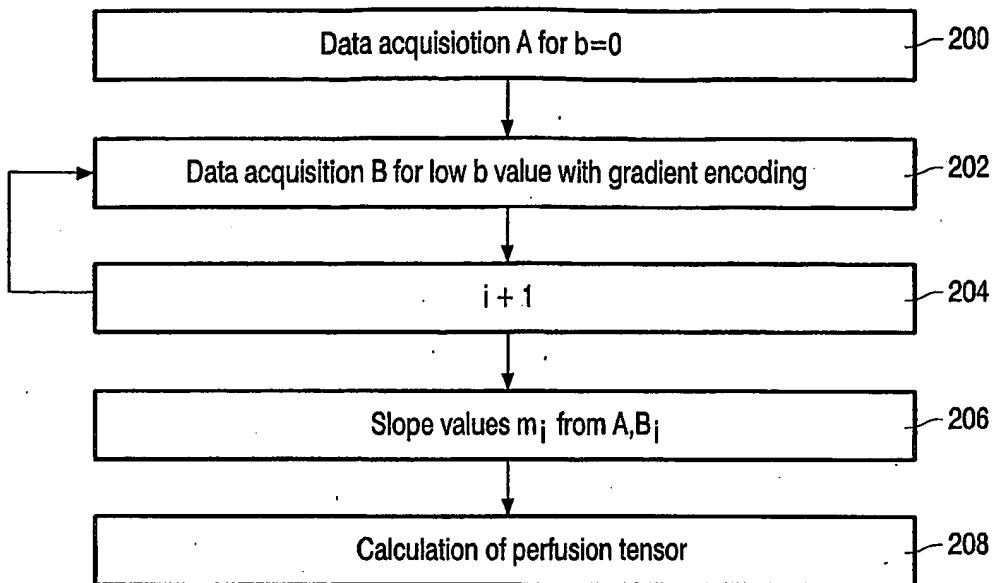


FIG. 2

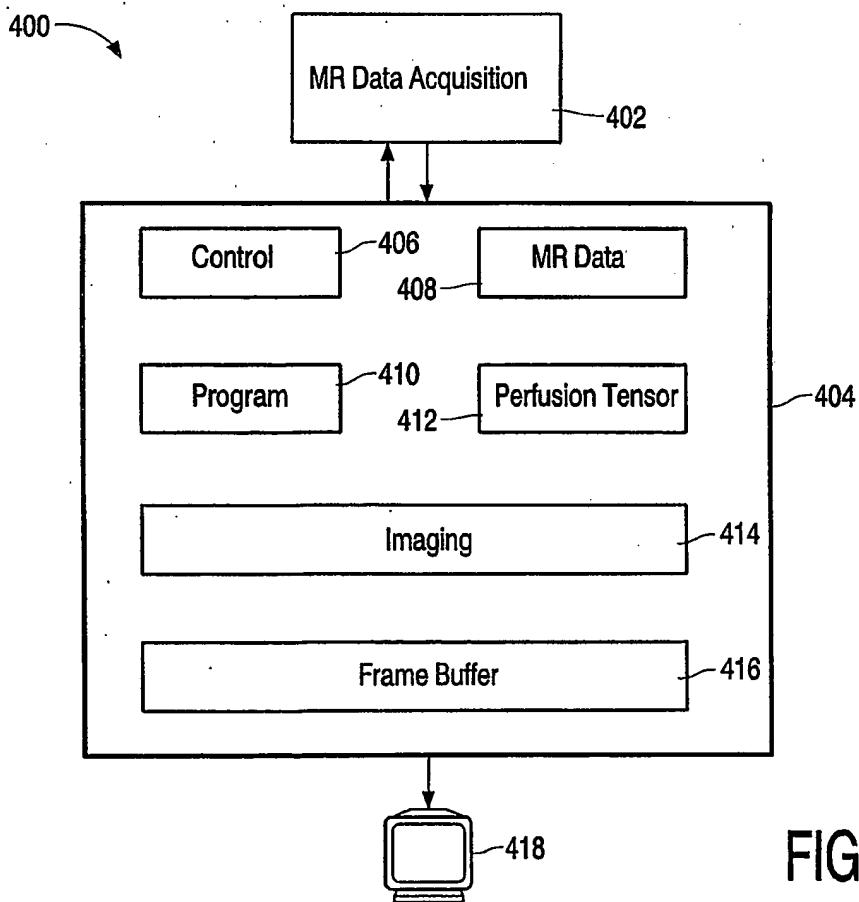


FIG. 4

3/3

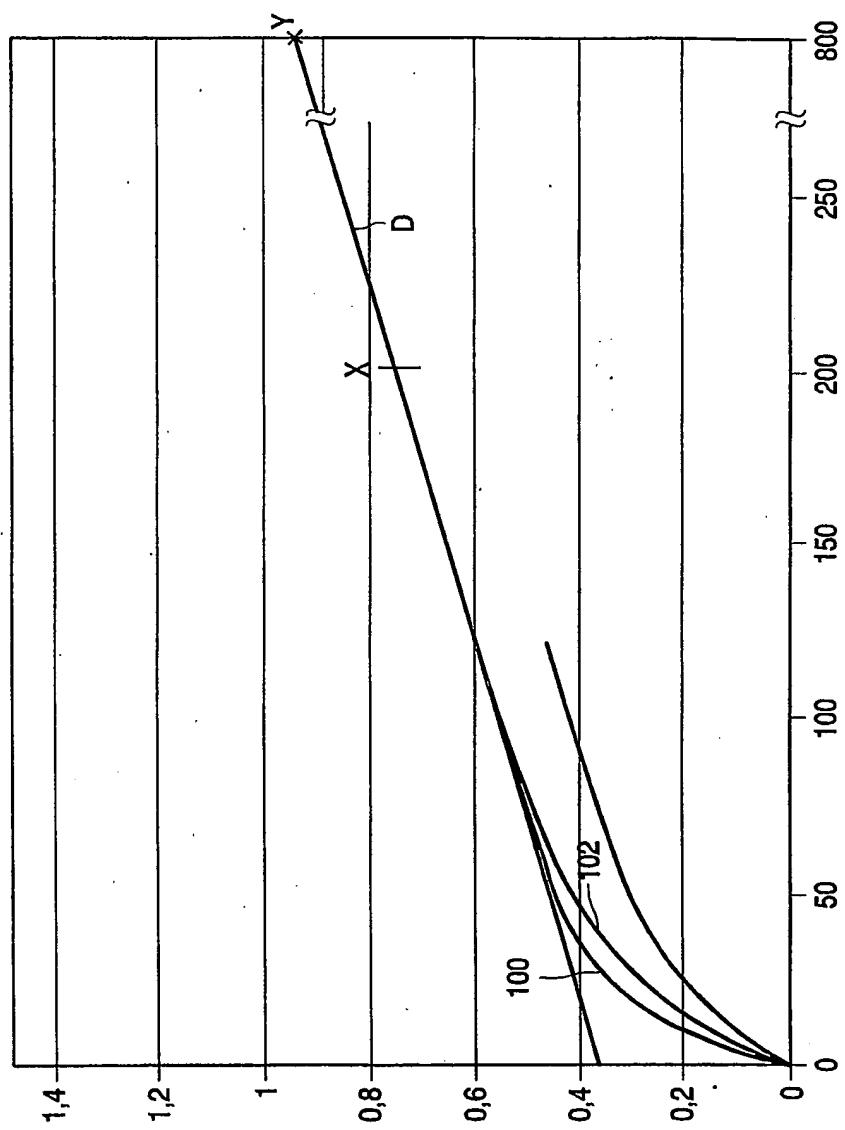


FIG. 3

INTERNATIONAL SEARCH REPORT

PCT/IB2004/050322

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 GO1R33/563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 GO1R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, INSPEC, COMPENDEX, WPI Data, EMBASE, MEDLINE, BIOSIS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, O, Y	<p>CALLOT V ET AL: "IVIM-based MRI method to study the microcirculation in the heart: preliminary results in dogs" PROCEEDINGS OF SPIE - THE INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING, MEDICAL IMAGING 2003. PHYSIOLOGY AND FUNCTION, METHODS, SYSTEMS AND APPLICATIONS, CONFERENCE 16.02.03-18.02.03, vol. 5031, May 2003 (2003-05), pages 214-221, XP002287611 USA ISSN: 0277-786X * chapter 2.3 *figure 3</p> <p style="text-align: center;">----- -/-</p>	1-17

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/050322

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BASSER P J ET AL: "ESTIMATION OF THE EFFECTIVE SELF-DIFFUSION TENSOR FROM THE NMR SPINECHO" JOURNAL OF MAGNETIC RESONANCE. SERIES B, ACADEMIC PRESS, ORLANDO, FL, US, vol. 103, no. 3, 1994, pages 247-254, XP000918072 ISSN: 1064-1866 the whole document	1-17
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